

**S/N 09/590884****PATENT****IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Appellant: Erika Hawkins et al.

Examiner: Ralph J. Gitomer

Serial No.: 09/590884

Group Art Unit: 1651

Filed: June 9, 2000

Docket: 341.014US1

Title: METHOD FOR INCREASING LUMINESCENCE ASSAY SENSITIVITY

**APPELLANT'S REPLY TO EXAMINER'S ANSWER****Mail Stop AF**

Commissioner for Patents

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This Appellant's Reply is presented in response to the Examiner's Answer to Appellant's Brief on Appeal, filed on August 27, 2002. Appellant's Brief on Appeal was filed in response to the final rejection of claims 1-57 of the above-identified application, as set forth in the Advisory Action mailed July 15, 2002.

The Appellant's Reply is filed in triplicate. Please charge any required additional fees or credit overpayment to Deposit Account 19-0743.

**ARGUMENT**

Claims 1-3, 8-12, 16-21 and 35-53 are not *prima facie* obvious over the disclosure of the cited *Mitoma* abstract. The Examiner has the burden under 35 U.S.C. § 103 to establish the *prima facie* obviousness of the claimed invention. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d (BNA) 1596, 1598 (Fed. Cir. 1988). None of the three elements required to establish a *prima facie* case of obviousness are present.

The Examiner has proffered no motivation for one skilled in the art to modify the haem or peroxidase enzyme system of the *Mitoma* abstract to yield a bio-luminescent assay as recited in the instant claims, nor does motivation exist. Additionally, the *Mitoma* abstract would not have provided one skilled in the art with a reasonable expectation that unwanted luminescence could be reduced, as recited in the instant claims, since the haem and peroxidase systems reported in the *Mitoma* abstract differ significantly from the assay systems described in the claims. Finally, the claims contain elements (e.g. specific assay types and specifically recited effects on signal and unwanted luminescence) not found in the *Mitoma* abstract. Thus, the claims are not *prima facie* obvious over the disclosure of the *Mitoma* abstract.

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**Claims 1-3, 8-31, and 34-57 are not *prima facie* obvious over the disclosure of *Kricka*.** *Kricka*, like the *Mitoma* abstract, relates to a chemiluminescent peroxidase system. As discussed in Appellant's Brief and hereinbelow, peroxidase systems differ significantly from the assay systems of the claims. The Examiner has provided no evidence that one skilled in the art would have recognized that any of the beneficial effects produced in the peroxidase systems of *Kricka* could be obtained in the claimed assay systems. Due to the significant differences in the mechanisms of light production between peroxidase systems and the claimed systems, Appellant submits that one skilled in the art would not have had a reasonable belief that similar effects could be produced. As with the *Mitoma* abstract, none of the elements needed to establish a *prima facie* case of obviousness exist. Thus, the claims are not *prima facie* obvious over the disclosure of *Kricka*.

**Claims 1-57 are not *prima facie* obvious over the disclosure of *Wood*.** *Wood* discloses a method for improving the kinetics of light production. *Wood* does not even discuss unwanted luminescence or methods for reducing unwanted luminescence. Thus, *Wood* provides no motivation to reduce unwanted luminescence as recited in the instant claims. Additionally, *Wood* would not have provided one skill in the art with a reasonable belief that unwanted luminescence could be selectively reduced. Finally, the instant claims recite selective quenching (for example, see claim 1: "reduces luminescence that is not dependent on the presence of an analyte by at least about 10 fold, and that reduces luminescence that is dependent on the presence of analyte by less than about 7 fold"). *Wood* provides no suggestion that such selectivity can be achieved. Thus, *Wood* does not disclose or suggest all the elements of the instant claims. Again, none of the three criteria required to establish a *prima facie* case of obviousness exist. Thus, claims 1-57 are not *prima facie* obvious over the disclosure of *Wood*.

Rebuttal to Examiner's AnswerMitoma

At page 5, line 7 (and lines 8-11) of the Examiner's Answer, reference is made to a "translation" of *Mitoma* (JP 07067696). It is respectfully submitted that no translation of *Mitoma* is of record. The *Mitoma* abstract was first cited in the Office Action mailed April 24, 2001; a

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copy of the abstract was provided, and the abstract was listed on the Form PTO-892. However, no translation of the *Mitoma* specification has previously been cited, provided to Appellant, or made of record. Appellant submits that the Examiner's reliance on specific portions of a *Mitoma* translation that is not of record represents a new ground of rejection. Thus, the Examiner's assertion in section (12) at page 9 of the Examiner's Answer is incorrect. Appellant asserts that the Examiner can not rely on portions of the previously un-cited *Mitoma* translation without reopening prosecution so the translation can be made of record and provided to Applicant for review.

At page 5 of the Examiner's Answer, the Examiner states that *Mitoma* teaches a method of decreasing background luminescence in chemiluminescent reactions but "not specifically in a method for decreasing background in a bioluminescent reaction." Thus, the Examiner admits that the peroxidase reaction described in *Mitoma* differs from the bio-luminescent reaction system recited in the claims. The Examiner goes on at page 5 to state that it would have been obvious from *Mitoma* to reduce background luminescence from any source because *Mitoma* teaches a general method of reducing background luminescence. The *Mitoma* abstract does not teach or suggest a "general method" for reducing background luminescence. Rather, the *Mitoma* abstract discusses certain specific peroxidase systems. There is no suggestion in the *Mitoma* abstract and no evidence of record to support the Examiner's conclusion that one skilled in the art would have reasonably believed the methods discussed in the *Mitoma* abstract could be applied to any other luminogenic systems.

As discussed in detail at pages 8 and 9 of Appellant's brief, there are significant differences between the peroxidase system discussed in *Mitoma* and the assay systems of the instant claims. The bio-luminescent assay systems of the instant claims (e.g., 1 and 3) utilize a bio-luminescent enzyme that has evolved for the purpose of generating light. Such enzymes have a binding pocket that holds the luminogenic substrate and excludes water while light is produced. The peroxidase discussed in the *Mitoma* abstract did not evolve specifically to produce luminescence, and the peroxidase does not possess a binding pocket that holds the substrate and excludes water while light is produced. Thus, each has a distinct chemical mechanism for making light, and one skilled in the art would not have a reasonable belief that the

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compounds discussed in *Mitoma* would have any beneficial effect in a bio-luminescent system. Accordingly, one skilled in the art would not have considered *Mitoma* to have taught a "general method" that could be applied to any luminescent system.

Kricka

At page 7 of the Examiner's Answer, in the first paragraph, the Examiner states that *Kricka* "does not specifically teach such a method in bio-luminescent reactions." Notwithstanding this admission, the Examiner goes on to conclude, without any supporting evidence, that "*Kricka* teaches a general process for increasing the signal/background ratio and decreasing background luminescence."

*Kricka*, like *Mitoma*, relates to peroxidase systems that differ significantly from the assays of the instant claims. Because of these differences, one skilled in the art would not have considered *Kricka*'s disclosure to have been generally applicable to bio-luminescent reactions. Thus, the Examiner's unsupported conclusion is incorrect.

Wood

At page 8 of the Examiner's Answer, in the first full paragraph, the Examiner states that *Wood* does not disclose that the sensitivity of an assay can be increased by reducing unwanted luminescence. As discussed above, *Wood* does not even discuss unwanted luminescence or methods for reducing unwanted luminescence. *Wood* discloses a method for improving the kinetics of light production. In spite of the Examiner's admission, he goes on to conclude that it would have been obvious to one having ordinary skill in this art to have utilized thiol reagents such as those taught by *Wood* to increase assay sensitivity since *Wood* teaches that thiol reagents decrease peak intensity and improve kinetics of light production.

The Examiner has provided no explanation or evidence that suggests that one skilled in the art would have believed there was any correlation between improved kinetics of light production and the claimed methods for increasing the sensitivity of an assay by decreasing unwanted luminescence. Without evidence that one skilled in the art would have reasonably believed that these two independent effects were closely correlated, the rejection can not be

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maintained. There is no such evidence in the record.

Other Points

The following additional remarks are presented to clarify other points raised in the Examiner's Answer for the record.

At page 10, line 16, the Examiner states, in light of the material at page 8 of the instant specification, "bioluminescence" is interpreted to mean "the emission of light from living organisms." For clarification, Appellant would like to point out that independent claims 1 and 3 recite a "bio-luminescent assay." For clarification, a bio-luminescent assay is an assay that utilizes one or more bio-luminescent enzymes. Further, a bio-luminescent enzyme is an enzyme, or a mutated derivative thereof, that has evolved in an organism by natural selection for the purpose of generating light (see the specification at page 8). Peroxidases did not evolve for the purpose of generating light.

At page 11 of the Examiner's Answer, the Examiner states "Much of Appellants arguments are centered upon unclaimed limitations, such as distinguishing luminescence as taught by the cited references in contrast to the presently claimed bioluminescence." Independent claims 1 and 3 recite a "bio-luminescent assay" in the preamble, and "the assay" is subsequently recited in the claim. Thus, independent claims 1 and 3 are clearly directed to bio-luminescent assays. It is not clear how the Examiner could believe this is an unclaimed element.

At page 11 of the Examiner's Answer, the Examiner states, "It would appear that there could be a genus/species issue at hand where the references teach the genus of luminescence and the claims are directed to a species of luminescence, bioluminescence." As discussed above, *Mitoma* and *Kricka* discuss specific peroxidase reactions. In light of the specific mechanistic features of these peroxidase systems, one skilled in the art would not have considered the method described in *Mitoma* or *Kricka* to be generally applicable to all luminogenic systems. Thus, the Examiner's suggestion that the bio-luminescent assays of the instant claims are a species of the peroxidase systems reported in the *Mitoma* abstract and in *Kricka*, is not supported in fact.

At page 12 of the Examiner's Answer, the Examiner takes the position that one skilled in the art would have a high expectation of success in employing a known method for assaying

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lysed cells to assay whole cells. Carrying out an assay in whole cells requires reagents and conditions that do not compromise cell integrity or viability. Additionally, carrying out an assay in whole cells requires reagents capable of penetrating cell walls. Thus, one skilled in the art would not reasonably assume that any assay that can be conducted with lysed cells could also be conducted with whole cells as suggested by the Examiner. The Examiner's conclusion is unsupported by any facts of record and it is not correct.

**CONCLUSION**

Appellant believes the claims are in condition for allowance and requests withdrawal of the rejections to claims 1-57. Reversal of the Examiner's rejections of claims 1-57 in this appeal is respectfully requested.

Respectfully submitted,

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**CERTIFICATE UNDER 37 CFR 1.8:** The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 12<sup>th</sup> day of May, 2003.

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